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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,755	05/22/2007	Vasant Jadhav	SIR-MIS-00004-US-PCT	5817

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
03/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/597,755	JADHAV ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *2,8-12,15-16,24-30,32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,13,14,17-23 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 11/19/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/19/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 11/19/2009, claims 1-32 are pending and claims 1, 3-7, 13, 14, 17-23 and 31 currently under examination in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-7, 13, 14, 17-23 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recite the multifunctional siNA comprise oligonucleotide strands of between 24 and 38 nucleotides wherein Z comprises nucleotides of 1-24 nucleotides, X comprise nucleotides of 1-24 and Y comprise nucleotides of 1-24 nucleotides. In any given strand of XZ or YZ, the total nucleotide length can be 48 nucleotides and that does not include the nucleotides of X' or Y'. It is unclear how each

strand can have a maximum length of 38 nucleotides but also comprise at least 48 nucleotides of XZ or YZ. Thus, the claims are indefinite and do not distinctly claim the subject matter.

New Claim Rejections - 35 USC § 103

Applicant's arguments filed in the response on 11/19/2009 will be addressed in the new rejection below.

Claims 1, 3-7, 13, 14, 17-23 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (US 2004/0053876), Tuschl et al. (US 20040259247), Rana et al. (US 2005/0020521), Parrish et al. (Molecular Cell, 2000, Vol. 6: 1077-1087), Pieken et al. (Science, 1991, Vol. 253: pages 314-317), Sullenger (US 20030083294), Matulic-Adamic (5,998,203), Braasch et al. (Biochemistry 2002, Vo. 41(14): 4503-4510) and evidenced by Caplen (Expert Opinion. Biol. Thera. 2003 Vol. 3(4) 575-586) and evidenced by Anderson et al. (Oligonucleotides 2003 of record cited on IDS filed 08/07/2006) and Leirdal et al. (Biochem and Biophys 2002 of record cited on IDS filed 08/07/2006).

The instant claims are drawn to a multifunctional siNA molecule of Formula I as shown wherein the siNA comprises terminal cap moieties and chemical modifications to purine and pyrimidine nucleotides wherein each one strand of the multifunctional siNA is complementary to a first target nucleic acid sequence and the second strand is complementary to a second target nucleic acid sequence.

Turner et al. teach siRNA molecules capable of inhibiting the expression of target genes and teach a multi-target siRNA comprising at least two antisense regions that are complementary to different target genes and that are complementary to sense regions on the opposite strands (sections X' and Y' of the instantly claimed molecule), and wherein the antisense that is adjacent to a sense strand can be a contiguous strand or separated by one to several nucleotides (see at least paragraph 218-219). Turner et al. teach the multitarget siRNA can comprise processing signals such that one or more duplex regions can be cleaved from the molecule (see paragraph 218). Turner et al. do not explicitly teach chemical modifications as instantly claimed.

Tuschl et al. teach a siRNA, 19-25 nucleotides in length, wherein each separate strand comprises at least 19 nucleotides complementary to the nucleotides of the other strand and wherein the 5'-terminus of the antisense strand comprises a phosphate and either strand or both comprise 3' nucleotide overhangs (see at least pages 1-5). Tuschl et al. additionally teach the nucleotides may be modified at the 2' position of the ribose sugar. Preferred modifications include 2'-O-methy, 2'-deoxy and 2' fluoro modifications and Tuschl et al. specifically teach each of the different preferred modifications may be combined in a single siRNA. Specific embodiments of modified siRNAs are taught in Fig. 14. Tuschl et al. teach compositions comprising siRNA and acceptable carriers (see page 3).

Likewise, Rana teach how to make siRNA molecules which are 10-50 nucleotides in length and preferably 18-25 nucleotides in length that are capable of directing or mediating RNA interference to any target gene (see paragraph 0070). Rana

further teach the siRNA can comprise a 5' phosphate group attached to the hydroxyl group of the 5' sugar (see paragraph 0059). Rana teach that such siRNA can be modified at internal residues such that properties such as chemical stability and nuclease resistance are improved without compromising the RNA interference activity (see paragraph 0029). Rana teach that the RNAi mechanism does not require 2'-OH chemical groups and these groups could be replaced with such nucleotides such as 2'-deoxy, 2'-O methyl and 2'-fluoro and the molecule was still able to efficiently induce RNAi in human cells. Rana teach the 3' terminal end or the 5' terminal end of the siRNA can be modified with such groups as peptides, cross linkers or organic compounds (see paragraph 0033). Rana teach pharmaceutical compositions comprising such siRNA (see paragraph 207). Rana teach the siRNA can comprise one or more chemical modifications in the sugar or nucleobase groups and teach the siRNA can comprise any combination of two or more modifications (see paragraphs 0036-0040). Rana teach that sense and/or antisense strands of such siRNA can comprise at least 100% of chemically modified nucleotides, which includes both purines and pyrimidines and specifically teach such siRNA comprising 100% of chemically modified nucleotides are stable (see Figure 12).

Parrish et al. teach a double stranded nucleic acid with an antisense or sense region comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides (see Figure 5) and further teach this double stranded nucleic acid can mediate degradation of cellular RNA (see abstract page 1082). Parrish et al. teach a chemically synthesized siRNA wherein each strand is 26 nucleotides in length.

The use of chemical modifications to increase the stability and target sequence recognition of an inhibitory nucleic acid molecule is well known in the art. Pieken et al. recognized the common problem inhibitory nucleic acids such as antisense compounds and ribozymes faced that stood in the way of their practical therapeutic applications. Pieken et al. teach modification of all pyrimidine nucleotides with 2'-fluoro groups imparted increased stability to a nucleic acid structure (see page 315). Pieken et al. teach ribozymes containing 2'-fluoro modifications at all pyrimidine positions were greatly stabilized against degradation and teach a systematic approach to testing said modifications in various positions on the molecule to determine the optimum position and number of nucleotides to modify to impart the most nuclease resistance to the molecule.

Sullenger et al. teach antisense oligonucleotides comprising modified linkages such as phosphorothioate and modified pyrimidines at the 2' position with 2'-O-methyl and/or 2'-fluoro. Sullenger et al. teach said modifications improve the in vivo stability and improve oligonucleotide delivery characteristics. Sullenger et al. further teach 3' and 5' end modifications such as capping.

Matulic-Adamic et al. found that incorporation of chemical modifications of ribozyme molecules can enhance the molecules nuclease resistance and in vivo stability. Matulic-Adamic et al. teach incorporation of chemical modifications protects the nucleic acid from degradation as well as improves bioavailability (see column 2) and specifically teach incorporation of 2'-doexy and 2'-deoxy 2'-fluoro modifications and exemplifies molecules comprising at least 50% of the nucleotides having modifications

(see column 3 and Figure 3). Matulic-Adamic et al. teach ribozymes comprising abasic terminal cap moieties that provide resistance to degradation (see columns 2-3). Matulic-Adamic et al. further teach the modifications can be in one or both strands and teach the molecule can comprise different types of chemical modifications in the same molecule. Matulic-Adamic et al. demonstrates the routine nature of incorporation of chemical modifications and testing said molecules to access the activity of said molecules (see entire specification).

Braasch et al. outlines the challenges faced with designing optimal inhibitory nucleic acid molecules for controlling gene expression. Braasch et al. teach that RNAi was emerging as a new approach to antisense gene inhibition and has already shown that gene inhibition is efficient and the toxicity is low (see page 4509). Braasch et al. states that if good in vivo uptake can be achieved using siRNA, then the use of RNAi could significantly improve the ability of oligonucleotides to have an impact on drug development. Braasch et al. teach certain goals for improving oligonucleotides and their applications which include improving pharmacokinetics and targeting and perform comparative studies to demonstrate the relative strengths of different oligomer chemistries (see Table 2). Braasch et al. teach that new oligonucleotide chemistries are available the possess chemical properties that can improve the molecules efficacy and highlights the necessity to continually improve inhibitory nucleic acids so the field will continue to generate new options for controlling gene expression.

It would have been obvious to generate the claimed siNA molecule and incorporate known modifications, such as 2'-O-methyl and/or 2'-fluoro, terminal cap

moieties and linker molecules to impart increased stability and functionality in any siRNA because it is well known to one of skill in the art that modifications of RNA with 2'-O-methyl and or 2'-flouro groups stabilize RNA and can protect RNA from nuclease degradation and one would be motivated to incorporate 2'-O-methyl groups to improve the efficacy of double stranded RNA.

Turner et al. teach various configurations of multi-target siRNA comprising multiple antisense regions that are capable of targeting different regions on one gene or multiple different genes simultaneously and describes each of the antisense regions and the complementary strands as inhibitory modules. In one embodiment Turner et al. teach the siRNA molecule can be designed such that the duplex regions comprising multiple inhibitory modules can be cleaved from the hairpin molecule that would generate the claimed multifunctional siRNA having separate strands. Thus, it would have been obvious to generate the claimed siNA molecule comprising at least two antisense strands. The claimed siNA molecule recites Z comprises nucleotides that are complementary between the antisense regions. Turner et al. teach the antisense regions can be separated by one to several nucleotides and these nucleotides would be complementary to the nucleotides on the opposite strand and could therefore bind a target molecule. Given the claimed siNA molecule does not recite a specific sequence, these nucleotides can be any nucleotide that is capable of being complementary to the target regions.

In response to Applicant's arguments that the rejection does not meet the standards of obvious to try as in discussed in In re Kubin because although there were

general guidelines to for designing a siRNA targeting a single gene, the design of a siRNA capable of targeting more than one gene was new. This argument is not convincing and incorrect. First it must be noted that Applicant's arguments addressing the unobviousness of the rejection starting on page 11 refers to the teachings of "Kubin". Kubin was not a cited reference and it appears the argument is directed to the Turner et al. and the response to this argument is based on this assumption.

In response to the argument that design of a siRNA capable of targeting more than one gene was not known in the art the Examiner has cited two references, Anderson et al. and Leideral et al., that teach multi-target short hairpin siRNA that were capable of initiating RNAi against multiple targets in cells and further discusses the advantages of using this type of siRNA molecule. While these references both teach sequence wherein the multiple antisense regions are in a short hairpin siRNA, the presence of a hairpin loop is a design choice for stability in generating said molecules and does not take away from the fact that a siRNA molecule is capable of targeting multiple genes simultaneously. Thus the instant invention is unobvious for at least the reason that it was known and demonstrated that a multi-target RNAi molecule is capable of targeting more than one gene simultaneously. Moreover, given that Turner et al. teach various configurations of a multi-target RNAi molecule, the instant invention would have been obvious to the skilled artisan.

A person of ordinary skill in the art would have wanted to incorporate modifications into the dsRNA and would have been able to predictably incorporate the various claimed modifications given these modifications were well known in the art and

routinely used by those skilled in the art for the purpose of enhancing nuclease resistance of a nucleic acid as demonstrated by Pieken et al., Matulic-Adamic et al. and Braasch et al. . A skill artisan, upon reading Tuschl et al. and Rana et al., would have recognized the advantages of incorporating chemical modifications into a siRNA, particularly at the 2' sugar positions and therefore based on the prior art, one of skill in the art would have been able to incorporate chemical modifications, such as 2'-O-methyl and/or 2'-fluoro to improve the in vivo stability of the nucleic acid and improve the nucleic acids delivery characteristics.

Applicant's arguments regarding the objective of Turner et al. was to provide a siRNA that can be enzymatically synthesized and produced inside the cell and therefore modifying this molecule would not be viable. This argument is not convincing because the dsRNA taught by Turner et al. is not limited to just enzymatic synthesis and there is no evidence pointed out by Applicant in the prior art or in Turner et al. that would lead one of skill in the art to think that incorporation of known modifications would lead to a molecule that was not viable. Moreover, the instant specification discloses that the claimed molecule with modifications can be chemically or enzymatically synthesized (see paragraph 0187). Thus one would have been able to create siRNA for the purpose of having increased stability and functionality in cells given Tuschl et al. teach siRNA as being useful in cell culture and in whole organisms for elucidating gene function in culture and in whole organisms, which may be considered to be nuclease-rich environments. It would have been obvious to chemically enhance the siRNAs resistance to nucleases while preserving or maximizing its activity in order to most

effectively target the desired gene and it would have been obvious to search for particular chemical modifications that are tolerated by the double stranded RNA by routine experimentation of determining the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to stability and functionality of the dsRNA. Moreover, one would have been motivated to incorporate 2'-deoxy-2'fluoro modifications into said siRNA because Parrish et al. specifically teach 2'-deoxy-2'fluoro modifications incorporated into dsRNA are compatible with RNAi activity (see page 1081).

Braasch et al. teach certain goals for improving oligonucleotides and their applications which include improving pharmacokinetics and targeting and perform comparative studies to demonstrate the relative strengths of different oligomer chemistries and because Braasch et al. teach that new oligonucleotide chemistries are available the possess chemical properties that can improve the molecules efficacy and highlights the necessity to continually improve inhibitory nucleic acids so the field will continue to generate new options for controlling gene expression, one would have clearly applied this to improving siRNA molecules using known chemical modifications that have been shown in the art to impart desirable characteristics onto inhibitory nucleic acid molecules.

In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the

Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.)

In the instant case, the all of the chemical modifications were known to one of ordinary skill in the art at the time the invention was made and the incorporation of said modifications into siRNA would have yielded nothing more than predictable results of improving the molecules nuclease resistance and stability to one of ordinary skill in the art at the time of invention. Therefore, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Further, it would have been obvious to one or ordinary skill in the art to incorporate chemical modifications in all of the nucleotide positions on one or both strands of said double stranded molecule as part of routine experimentation to further increase the efficacy of said molecules. Moreover, because Matulic-Adamic et al. teach terminal cap moieties provide nuclease resistance and protection from degradation and since each of the modifications were known to increase efficiency of oligonucleotide delivery and stability, one would have been able to predictable make double stranded molecules comprising terminal cap moieties.

The motivation to chemically modify double stranded molecules is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring

an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate each of the above-mentioned modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1390 (U.S. 2007) the Supreme Court found, "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."

At the time the instant invention was made it was known that nucleic acid molecules were subject to nuclease degradation and decreased target affinity and it was also known that incorporation of a finite number of identified chemical modifications such as 2'-O-methyl and/or 2'-fluoro on specific nucleotides could greatly enhance a nucleic acid molecules ability to be resistance to degradation and have enhanced bioavailability and target specificity. Therefore, it would have been obvious to one of ordinary skill in the art to try, with a reasonable expectation of success, incorporation of known chemical modifications into double stranded molecules and a matter of routine experimentation to determine the optimum number and position of each modification.

One would have a reasonable expectation of success given that Tuschl et al. and Rana et al. teach how to make and use virtually any siRNA to any gene provided the

target sequence is known and teach that methods of RNA synthesis are known in the art, as evidenced by the examples provided therein. Further, one would have a reasonable expectation of success because chemical modifications of an oligonucleotide, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made. Additionally, one would expect such modifications would benefit double stranded molecules because such modifications had been shown to benefit antisense or ribozymes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 103

The rejection of claims 1, 3-7, 13, 14, 17-23 and 31 under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (US 2004/0053876), Tuschl et al. (US 20040259247), Rana et al. (US 2005/0020521), Parrish et al. (Molecular Cell, 2000, Vol. 6: 1077-1087), Pieken et al. (Science, 1991, Vol. 253: pages 314-317), Sullenger (US 20030083294), Matulic-Adamic (5,998,203), Braasch et al. (Biochemistry 2002, Vo. 41(14): 4503-4510) and evidenced by Caplen (Expert Opinion. Biol. Thera. 2003 Vol. 3(4) 575-586) is withdrawn in view of the new rejection above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Fereydoun Sajjadi at 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Kimberly Chong/
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